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Review Article

Evening Administration of Sglt2 Inhibitors May Be More Efficacious in Preventing Night time Hyperglycemic Variability

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Abstract

The rotation of the earth it-self is responsible for day and night rhythms of biomarkers that are important in the physiology and metabolic functions in health and disease. A therapeutic agent may be highly bioavailable but may not be bioactive due to alterations in day and night metabolic rhythms and chrono-pharmacokinetics of the agent. A landmark experiment reported the structure and mechanism of action of the sodium glucose transporters (SGLT) proteins in relation to longevity. This evidence is of high significance because SGLT2 inhibiters are highly effective in the treatment of diabetes mellitus (DM) and cardiovascular diseases (CVDs). Glucose may be absent in the urine due to reabsorption of filtered glucose, in the kidney tubules via SGLT proteins, and metabolized by increased nighttime release of insulin. SGLT1 mRNA level is maximum at dark and hepatocyte nuclear factor-1 beta binding exhibits the circadian periodicity of SGLT1 proteins, whereas MAP 17 activates SGLT-2 in the dark. The mRNA transcription for ribosomal proteins for SGLT and ribosomal loading occur at night. In a recent study, the effects of chronotherapy with a SGLT2 inhibitor empagliflozin (EMPA) was examined, in 23 patients with type 2 DM. Treatment with EMPA in the evening or morning showed significant decline in nightly blood glucose, fasting and post prandial blood glucose, HbA1C and blood pressure in both groups. However, therapy with EMPA in the evening resulted in greater reductions in all these markers, compared to morning administration. The results indicate that night time administration of SGLT2 inhibitors may be more efficacious.

Keywords: *Sodium Glucose Transporters; Diabetes Mellitus; Glucose; Day; Night*

Introduction

The value of night time hypertension causing increased risk of cardiovascular diseases (CVDs) is known, however, the role of circadian increase in blood glucose and oxidative stress is not well recognized as risk factor of CVDs. The circadian determinants of nocturnal rhythms of increase in blood glucose and\or night time glycemic variability and oxidative stress causing antioxidant deficiency of endogenous antioxidants has not been stressed. Sodium glucose transporters 2 (SGLT 2) inhibitors are frequently used in patients with type 2

diabetes mellitus (T2DM) and CVDs, because these agents have been found to have potential antioxidant activity. The expression of SGLT proteins in various cells, kidney tubules and gut occurs in the night, which indicates that bioactivity of SGLT2 inhibitors may occur in a circadian fashion [1,2]. The bioactivity of a therapeutic agent depends on chrono-pharmacokinetics of the agent, because it may be highly bioavailable but may not be highly bioactive. It has been proposed that day and night rhythms with reference to time of therapy determine the bioactivity of SGLT2 inhibitors. Recently, a landmark study reported the structure and mechanism of action of the SGLT proteins, with reference to SGLT2 inhibitors, which prompts us to comment further on these molecules [3] (Han., *et al,* Nature 2021).

Nocturnal expression of sodium glucose transporter proteins

The increased expression of SGLT proteins in the night in the tissues may be crucial in the determination of circadian bioactivity of SGLT2 inhibitors. SGLT proteins 1 and 2 are normally present in the intestines, liver, kidney, heart, pancreas, brain and arteries to maintain the circadian physiology and metabolism of these organs [1,2,4,5]. In addition, SGLT2s are also located in pancreatic alpha-cells and in the cerebellum [4]. However, SGLT1s are more widely distributed in kidneys, intestine, heart, lungs and skeletal muscles, but both the proteins are expressed predominantly in the night as these are considered repairing molecules [1,2]. Previous studies have focused on the regulation of SGLT expression under different metabolic and pathophysiological conditions, for example western or Mediterranean diet, age, obesity, sleep disorders or nighttime activity as well in patients with T2DM [1,2,4,5]. In T2DM and in malabsorption syndromes, the elevated renal threshold for glycosuria and increased renal glucose reabsorption capacity, appear to be due to the increased expression of SGLT2s in tubular epithelial cells [3-6]. This mechanism represents an adaptation, to prevent loss of energy, contributing to the multifunctional pathogenesis of hyperglycemia in subjects with T2DM.

Behavioral factors.	Biological factors
Short sleep/disturbed sleep.	Melatonin and glucagon deficiency.
Night awakening/OSA	Increased ghrelin/more appetite.
Sleep debt.	Obstructive sleep apnea.
Night time eating.	Insulin resistance, hyperglycemia.
Mental stress in the night.	Increased cortisol, low nitric oxide release
Physical activity in the night.	Increased cortisol.
Tobacco, alcohol, caffeine.	Night hypertension/no dipping.
Western diet.	Leptin and adiponectin deficiency
	Oxidative stress and inflammation.
	Decrease in growth hormones.
	Increased risk of obesity, diabetes and cardiovascular diseases.
	Increased expression of SGLT proteins.
	Endothelial and SMC dysfunction

Table 1: *Circadian determinants of nocturnal risk of cardiovascular diseases.*

Chronophysiology of SGLT proteins

It has been reviewed that the regulation of SGLT proteins occurs via certain pathways involving cyclic adenosine monophosphate/protein kinase A, protein kinase C, glucagon-like peptide 2, insulin, leptin, signal transducer and activator of transcription-3 (STAT3), phosphoinositide-3 kinase (PI3K)/Akt, mitogen-activated protein kinases (MAPKs), nuclear factor-kappaB (NF-kappaB), with-no-K [Lys]

kinases/STE20/SPS1-related proline/ alanine-rich kinase (Wnk/SPAK) and regulatory solute carrier protein 1 (RS1) [2-7]. A study in rats showed that SGLT1 mRNA level is maximum near the onset of dark and minimum near the onset of light [1]. It seems that hepatocyte nuclear factor-1 beta binding exhibits the circadian periodicity of SGLT1 proteins and MAP 17 activates SGLT-2 in the dark [2]. There is nocturnal occurrence of transcription and translation of mRNA for ribosomal proteins for SGLT and mitochondrial respiration [2]. It is proposed that the circadian periodicity functions at the cell level may produce ribosome loading in the night due to the circadian clock dysfunction. Glucose remains absent in the urine due to reabsorption of filtered glucose in the kidney tubules via SGLT proteins that are expressed in the night along with nocturnal release of insulin, to metabolise reabsorbed glucose, for growth and repair [1,2,5].

SGLT2 inhibitors for chronotherapy of nocturnal hyperglycemia

SGLT2 inhibiters are considered the latest advancement in the treatment of T2DM [9]. It may be of high relevance to demonstrate the circadian bioactivity of these agents [11-13]. In a clinical study, treatment with empagliflozin (EMPA) was found to decrease blood pressure in dipper and non-dipper patients with T2DM and hypertension [11]. In a post-hoc analysis, among 12 patients with hypertension and T2DM, adjusted mean (SE) changes from baseline in mean 24-hour systolic BP (mm Hg) at week 12 were - 0.2 (0.7) with placebo vs -3.8 (0.6) and - 3.9 (0.7) with EMPA 10 and 25 mg, respectively (both $P < .001$ vs placebo) among dippers [11]. However, in non-dippers, these changes were 1.0 (0.7) with placebo vs -1.6 (0.7) with EMPA 10 mg ($P = .013$ vs placebo) and -3.8 (0.7) with EMPA 25 mg ($P < .001$ vs placebo). Both systolic and diastolic patterns of BPs among both dippers and non-dippers, were maintained over 24 hours [11].

In another study, patients with T2DM receiving EMPA (25 mg/day); in the evening (n = 25) or morning (n = 23), mean concentrations of nighttime blood glucose, fasting and post prandial blood glucose, HbA1C and blood pressures revealed a significant decline, in both the groups [14]. However, therapy with empagliflozin in the evening caused greater reduction in all these markers compared to a decrease with morning therapy. The odds ratios for night, 0.92 (0.83 - 1.02, $P < 0.01$), morning 0.79 (0.71 - 0.90, $P < 0.01$) and post prandial blood glucose 0.91 (0.82 - 1.10, $P < 0.01$) and HbA1c 0.79 (0.70 - 0.89, $P < 0.01$) and systolic 0.98 (0.87 - 1.11, $P < 0.05$) and diastolic 0.97 (0.86 - 1.12, $P < 0.05$) blood pressures, were significantly correlated with decreased night-time risk and modestly with morning-time risk. It is clear that therapy with EMPA in the evening was associated with significantly better efficacy compared to morning therapy suggesting that appropriate chronotherapy with SGLT2 inhibitors can inhibit SGLT2 expression more effectively.

A recent study found that in diabetes mellitus, changes in circadian machinery in monocytes underlies chronic kidney disease-associated cardiac inflammation and fibrosis [15]. Several studies have demonstrated that SGLT2 inhibitors can cause significant decline in blood glucose as well as provide benefits in reducing body weight, insulin resistance, lipid profiles and blood pressure [15,16]. Further studies indicate, that SGLT2 inhibitors empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin can decrease the rates of major adverse cardiovascular events and of hospitalization for heart failure in T2DM patients regardless of CVD [16]. The potential mechanisms of SGLT2 inhibitors on cardio-protection may be involved in improving the function of beta cells of pancreas, smooth muscle cell and vascular endothelial cells, suppressing oxidative stress, inhibiting inflammation and regulating autophagy, protecting from atherosclerosis. It is possible that in all of these biological mechanisms, circadian dysfunction in the peripheral clocks of the concerned cells, is crucial in the pathogenesis of damage to these organs. Therefore, it may be proposed that SGLT2 inhibitors may also act by regulating the circadian clock function, which is apparent from our observation [14].

It has been also reported that there is brainstem integration of arousal, sleep, which can influence cardiovascular, and respiratory control via maintaining sleep and wakefulness [17,18]. It seems that the function of sleep, includes; somatic and brain development, neuronal function, energy conservation, sentinel, and survival function as well as. regulation of BP and HR and possibly blood glucose and neurohormonal dysfunction [19]. It is known that blood glucose level is maintained within very narrow limits with less than 5% variability at a given time of the 24 hour day. Blood glucose level may alter with almost 50% difference over the circadian cycle due to influence of environmental and endogenous factors. It is not clear, how the circadian clocks in the brain and peripheral clocks regulate these light-dark variations with such tiny disparities. It has been found that via vasopressin release at the beginning of the sleep phase, the central suprachiasmatic nucleus increases the glucose transporter GLUT1 in tanycytes [19]. The GLUT1 in turn activates glucose entry into the arcu-

ate nucleus, thereby reducing peripheral glucose levels. Thus, by blocking the activity of vasopressin or the action of GLUT1 transporter at the daily trough of blood glucose level enhances circulating glucose levels often observed at the peak of the rhythm. It is clear that mechanisms regulated by circadian clock promoting glucose entry into the arcuate nucleus explain the cause of lower peripheral blood glucose before onset of sleep. The value of night time increase in blood pressures**,** compared to day time, due to nocturnal hyperglycemia as determinant of morbidity and mortality has already been proven [20]. It is high time to consider night time blood glucose as important hyperglycemic glucose variability disorder, for prevention of morbidity and mortality due to CVDs and T2DM. It seems that administration of drug in the evening would not have a nocturnal hypoglycemic effect.

Conclusions

The greater availability of SGLT proteins in the night implies that chronotherapy with SGLT2 inhibitors, targeting nocturnal determinants of risk due to nocturnal increase in biomarkers such as hyperglycemia, and pro-inflammatory cytokines, as well as blood pressures, when these markers are in highest concentration, may provide better efficacy with minimal side effects.

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